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Determinants of Mortality from Severe Dengue in Brazil: A Population-Based Case-Control Study

Giselle Hentzy Moraes,* Eliane de Fátima Duarte, and Elisabeth Carmen Duarte

State Health Department of the Federal District, University Hospital, University of Brasília, Pan American Health Organization, Brasília, Brazil

Abstract. Although increases in severity of mortality from dengue infection have been observed in Brazil, their determinants are not fully known. A case–control study was conducted by using the National Notifiable Diseases Surveillance System, including patients with severe dengue during 2000–2005. Cases were defined as patients that died and controls were those who survived. Hierarchical multivariate logistic regression was performed. During the study period, there were 12,321 severe cases of dengue and 1,062 deaths. Factors independently associated with death included age ≥ 50 years (odds ratio [OR] = 2.29, 95% confidence interval [CI] = 1.59–3.29), < 4 years of schooling (OR = 1.83, 95% CI = 1.47–2.28), a rural area (OR =2.84, 95% CI = 2.19–3.69), hospitalization (OR = 1.42, 95% CI = 1.17–1.73), and a high hematocrit (OR = 2.46, 95% CI = 1.85–3.28). Factors associated with a lower chance of dying were female sex (OR = 0.76, 95% CI = 0.67–0.87), history of previous dengue (OR = 0.78, 95% CI = 0.62–0.99), positive tourniquet test result (OR = 0.47, 95% CI = 0.33–0.66), laboratory diagnosis of dengue (OR = 0.75, 95% CI = 0.61–0.92), and a platelet count of 50,000–100,000 cells/mm^3 (OR = 0.56, 95% CI = 0.36–0.87). The risk profile identified in this study should serve to direct public health interventions to minimize deaths.

INTRODUCTION

The World Health Organization has estimated that dengue viruses infect > 50 million persons worldwide each year. A total of 1% of these persons are given a diagnosis of dengue hemorrhagic fever (DHF) and of these persons, the disease causes death in approximately 4% of the cases.[1] Potts and others estimated that the annual number of dengue cases varies between 70 million and 500 million.[2] Ongoing monitoring provided by the Pediatric Dengue Vaccine Initiative estimates that 55% of the world's population (3.6 billion persons) are at risk for dengue in 124 countries, and of 36 million cases per year, 6% (2.1 million) will develop DHF and show a case-fatality rate for DHF of 1% (21,000 deaths).[3]

A person with a typical case of DHF has high fever, hemorrhagic phenomena, and often hepatomegaly and signs of circulatory failure. Some patients may show development of dengue shock syndrome (DSS), which is characterized by hypovolemic shock resulting from plasma leakage, and can be fatal if not identified early and treated promptly and appropriately.[4]

Secondary dengue infection with another serotype, white race, female sex, age at infection < 15 years, and previous diagnosis of chronic disease have been documented as risk factors for development of DHF and DSS.[5–9] However, the pathogenic mechanisms of the disease have not yet been fully elucidated, and there is still controversy about other potential predictors of poor prognosis.[10,11]

During the past 10 years in Brazil, there has been a steady increase in the number of hospitalizations, diagnosis of severe disease and deaths from dengue.[12] These findings may be partly explained by a change in disease pattern characterized by hyperendemicity, simultaneous circulation of all four dengue virus serotypes (DENV1, DENV2, DENV3, and DENV4), and lack of awareness or training of the attending medical professional.[12]

Ideally, the case-fatality rate of DHF should be lower than 1%, but it can be as high as 20% in the absence of prompt diagnosis and proper treatment.[13,14] In Brazil, the case-fatality rate of DHF has remained above 5% in recent years.[15] This proportion is substantially higher than the ideal figure (< 1%), a fact that prompted us to investigate the causes for this excess mortality to identify interventions that could lead to improved outcomes.

MATERIALS AND METHODS

The study population consisted of all persons with severe dengue registered in the National Notifiable Diseases Surveillance System (SINAN) during January 1, 2000–December 31, 2005. In Brazil, dengue is a notifiable disease and SINAN, which was implemented throughout Brazil in 1990, should include all symptomatic cases of dengue, severe or not severe, identified by public or private health services. Case confirmation can be made by using clinical, epidemiologic, or laboratory criteria, and the proportion of laboratory confirmation among severs dengue cases is > 50%. Patients with severe dengue cases were all dengue patients who died and/or were classified as having DHF, DSS, or dengue with complications.

A population-based case–control study was conducted in which cases were dengue patients who died, and controls were dengue patients who recovered from the acute disease. Dengue patients with no information on disease outcome were excluded. Analysis variables were restricted to the set of variables available in SINAN. Whenever necessary, an unknown category was created to include missing and/or ill-defined classifications.

The period of notification was divided into two-year groups and each biennium was classified as epidemic or non-epidemic periods. The biennium 2002–2003 was considered epidemic because it had the largest number of notifications within the study time series.

A state of notification and presumed state of infection were compared and a categorical variable was generated (same or different states). Our hypothesis regarding this variable was that when these states are not the same, the health services located on the notification area may not be aware of the epidemiologic status of the place of infection of the patient.

A hierarchical approach was used as the causal theoretical model for determinants of deaths caused by severe dengue as

*Address correspondence to Giselle Hentzy Moraes, SHIS QI 25, Conjunto 02, Casa 09, Brasília DF, Brazil CEP 71660-220. E-mail: giselle.hm@gmail.com

follows.[16] The first hierarchical level included demographic, social, and epidemiologic variables (sex, age group, schooling, race/color, and period of notification). The second hierarchical level added variables of access to health services and care (history of vaccination against yellow fever, place of residence, history of hospitalization, region of notification, notification state, and history diagnostic laboratory tests for dengue). The third hierarchical level added variables of early signs of severity (history of previous dengue infection, number of early symptoms of severity [headache, exanthema, retro-orbital pain, prostration, myalgia, nausea/vomiting, arthralgia and diarrhea], tourniquet test results, mild bleeding, and time interval between onset of symptoms and case notification). The fourth hierarchical level added variables of late signs of severity (hematuria, upper gastrointestinal bleeding, number of warning signs [severe abdominal pain, arterial hypotension, neurologic manifestation, painful hepatomegaly, hypovolemic shock, hepatic failure, and myocarditis], high hematocrit, cavitary effusion, and low platelet count).

Univariate and multivariate logistic regression models with or without a hierarchical approach were constructed to assess the association between independent factors and outcome. The measures of strength of the associations used were the crude odds ratio" (OR_C), the OR from the multivariate analysis with hierarchical approach (OR_H) and the OR from a final logistic regression model ignoring the hierarchy of the variables (fully adjusted OR = OR_F). In all cases, the backwards technique to remove the irrelevant variables was used.[17] The Wald test was performed for all variables, and statistical level of significance was set at $P < 0.05$. SPSS version 15.0 (SPSS IBM, Armonk, NY) and STATA version 8.2 (StataCorp LP, College Station, TX) were used for data analyses.

The study protocol was approved by the Brazilian Ethics Committee. Authorization was granted by the Ministry of Health.

RESULTS

During 2000–2005, there were 12,321 cases of severe dengue (the study population) reported to SINAN. Among them, 1,062 (8.6%) patients died (cases) and 11,259 (91.4%) recovered completely (controls). Most patients were women (58.9%), 15–49 years of age (69.8%), lived in urban areas (92.6%) and in the West Central region (38.9%). Cases (1,062 deaths) were also predominantly women (52.8%), 15–49 years of age

TABLE 1

Descriptive characteristics of severe dengue cases reported to the National Notifiable Diseases Surveillance System by outcome (deaths and no deaths), Brazil, 2000–2005

Characteristic	Deaths (n = 1 062)		No deaths (n = 11,259)		Total (n = 12,321)	
	No.	%	No.	%	No.	%
Sex						
M	501	47.2	4,558	40.5	5,059	41.1
F	561	52.8	6,701	59.5	7,262	58.9
Age group, years						
0–14	143	13.5	1,760	15.6	1,903	15.4
15–49	645	60.7	7,951	70.6	8,596	69.8
≥ 50	271	25.5	1,544	13.7	1,815	14.7
Missing	3	0.3	4	0.0	7	0.1
Race/color						
White	212	20.0	3,481	30.9	3,693	30.0
Black/Brown	258	24.3	2,645	23.5	2,903	23.6
Yellow	7	0.7	129	1.1	136	1.1
Indigenous	0	0.0	15	0.1	15	0.1
Missing	585	55.1	4,989	44.3	5,574	45.2
Schooling, years						
≥ 4	386	36.3	5,118	45.5	5,504	44.7
< 4	136	12.8	902	8.0	1,038	8.4
Not applicable*	117	11.0	1,416	12.6	1,533	12.4
Missing	423	39.8	3,823	34.0	4,246	34.5
Place of residence						
Urban	907	85.4	10,503	93.3	11,410	92.6
Rural	103	9.7	259	2.3	362	2.9
Missing	52	4.9	497	4.4	549	4.5
Period of notification						
2002–2003	626	58.9	8,391	74.5	9,017	73.2
2000–2001	240	22.6	1,267	11.3	1,507	12.2
2004–2005	196	18.5	1,601	14.2	1,797	14.6
Region of notification						
West Central	105	9.9	4,692	41.7	4,797	38.9
Northern/Northeastern	583	54.9	3,479	30.9	4,062	33.0
Southeastern	355	33.4	2,810	25.0	3,165	25.7
Southern	16	1.5	60	0.5	76	0.6
Missing	03	0.3	218	1.9	221	1.8
Signs and symptoms†						
Fever and 2 symptoms	92	8.7	445	4.0	537	4.4
Fever and 3–5 symptoms	470	44.3	4,527	40.2	4,997	40.6
Fever and 6–8 symptoms	362	34.1	5,879	52.2	6,241	50.7
No fever or < 2 symptoms	138	13.0	408	3.6	546	4.4

*Years of schooling for children < 15 years of age.
†Headache, exanthema, retro-orbital pain, prostration, myalgia, nausea/vomiting, arthralgia, and diarrhea.

TABLE 2
Association between death from severe dengue and demographic, social, and epidemiologic characteristics, Brazil, 2000–2005*

Characteristic†	Univariate analysis		Multivariate, First HL			Multivariate FM		
	OR_C	95% CI	OR_H	95% CI	Wald test	OR_F	95% CI	Wald test
Sex								
M	1.00	Referent	1.00	Referent		–	–	
F	0.76	0.67–0.86	0.76	0.67–0.87		–	–	
Age group, years								
0–14	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
5–49	0.99	0.82–1.20	1.15	0.81–1.64		1.18	0.80–1.75	
≥ 50	2.16	1.74–2.67	2.29	1.59–3.29		2.01	1.34–3.04	
Missing (0.05%)	9.23	2.04–41.64	7.46	1.58–35.25		1.29	0.24–6.79	
Schooling, years								
≥ 4	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	0.028
< 4	1.99	1.62–2.46	1.83	1.47–2.28		1.44	1.12–1.84	
Not applicable‡	1.09	0.88–1.35	1.40	0.94–2.08		0.99	0.63–1.53	
Missing (34.5%)	1.46	1.27–1.69	1.34	1.14–1.58		1.02	0.85–1.22	
Race/color								
White	1.00	Referent	1.00	Referent	< 0.001	–	–	
Black/Brown	1.60	1.32–1.93	1.52	1.25–1.84		–	–	
Yellow	0.89	0.41–1.93	0.86	0.39–1.89		–	–	
Indigenous	–	–	–	–		–	–	
Missing (45.29%)	1.92	1.63–2.26	1.54	1.27–1.87		–	–	
Period of notification								
2002–2003	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	0.006
2000–2001	2.53	2.16–2.97	2.26	1.88–2.71		1.04	0.83–1.31	
2004–2005	1.64	1.38–1.94	1.64	1.38–1.95		1.40	1.13–1.73	

*HL = hierarchical level; FM = final model ignoring the hierarchy; OR_C = crude odds ratio; CI = confidence interval; OR_H = hierarchical odds ratio; OR_F = fully adjusted odds ratio.
†Values in parenthesis are proportion of missing data in the final model (n = 12,306).
‡Years of schooling for children < 15 years of age.

(60.7%), lived in the urban area (85.4%) and most (54.9%) were from Northern and Northeastern regions (Table 1).

Results of hierarchical approach multivariate logistic regression models after adjustment for variables from the first hierarchical level are shown in Table 2. A significantly higher chance of death from severe dengue was associated with an age ≥ 50 years ($OR_{(h)}$ = 2.29), < 4 years of schooling ($OR_{(h)}$ = 1.83), black/brown race/color ($OR_{(h)}$ = 1.52) and case notification reported before ($OR_{(h)}$ = 2.26) or after ($OR_{(h)}$ = 1.64) the epidemic period. Women had a significantly lower chance of

TABLE 3
Association between death from severe dengue and access to health service characteristics, Brazil, 2000–2005*

Characteristic†	Univariate analysis		Multivariate, Second HL			Multivariate FM		
	OR_C	95% CI	OR_H	95% CI	Wald test	OR_F	95% CI	Wald test
Yellow fever vaccine								
No	1.00	Referent	1.00	Referent	< 0.001	–	–	
Yes	0.44	0.36–0.52	1.11	0.90–1.35		–	–	
Missing (36.44%)	1.28	1.10–1.49	1.48	1.25–1.74		–	–	
Place of residence								
Urban	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Rural	4.60	3.62–5.84	2.84	2.19–3.69		2.07	1.57–2.74	
Missing (5.27%)	1.21	0.90–1.62	1.23	0.90–1.67		1.13	0.81–1.57	
Hospitalization								
No	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Yes	2.41	2.01–2.88	1.42	1.17–1.73		1.59	1.26–1.98	
Missing (38.01%)	2.47	2.09–2.92	1.31	1.06–1.61		1.00	0.79–1.27	
Region of notification								
West Central	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Northern/ Northeastern	7.48	6.05–9.25	4.47	3.50–5.70		2.33	1.78–3.05	
Southeastern	5.64	4.51–7.05	3.59	2.80–4.62		2.68	2.04–3.51	
Southern	11.91	6.64–21.37	10.77	5.78–20.05		4.76	2.42–9.36	
Missing (1.79%)	0.61	0.19–1.95	0.74	0.23–2.36		1.13	0.32–3.88	
State of notification and infection								
Same	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Different	1.63	1.08–2.46	2.34	1.50–3.65		1.97	1.18–3.27	
Missing (54.2%)	0.50	0.44–0.57	0.72	0.62–0.83		0.62	0.53–0.73	
Laboratory diagnosis‡								
No	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Yes	1.24	1.03–1.49	0.75	0.61–0.92		0.79	0.63–0.99	
Missing (25.58%)	2.93	2.45–3.51	1.49	1.21–1.84		1.37	1.09–1.72	

*HL = hierarchical level; FM = final model ignoring the hierarchy; OR_C = crude odds ratio; CI = confidence interval; OR_H = hierarchical odds ratio; OR_F = fully adjusted odds ratio.
†Values in parenthesis are proportion of missing data in the final model (n = 12,306).
‡Laboratory diagnosis of dengue included serologic analysis (IgM), viral isolation, histopathologic analysis, immunohistochemical analysis, reverse transcription–polymerase chain reaction, and another nonspecified test.

dying from severe dengue than men ($OR_{(h)}$ = 0.76). Patients with unknown age, level of education, or race/color also had a significantly higher chance of death.

Results from models adding the variables from the second hierarchical level multivariate logistic regression model while controlling for the relevant variables from the first hierarchical level are shown in Table 3. Persons with a significantly higher risk of death were those with an unknown history of yellow fever vaccination ($OR_{(h)}$ = 1.48), residents of rural areas ($OR_{(h)}$ = 2.84) with a positive ($OR_{(h)}$ = 1.42) or unknown ($OR_{(h)}$ = 1.31) history of hospitalization, whose cases were notified in any region other than the West Central (Southern $OR_{(h)}$ = 10.77, Northern/Northeastern $OR_{(h)}$ = 4.47, the Southeastern $OR_{(h)}$ = 3.59) region. A higher risk of death from a severe dengue was also detected when there was mismatch of state of notification and presumed state of infection (i.e., they were different) ($OR_{(h)}$ = 2.34). Having had a diagnostic laboratory examination for dengue was associated with a decreased in risk of death ($OR_{(h)}$ = 0.75).

Results from models taking into account variables from the third hierarchical level and controlling for relevant variables from the first and second hierarchical levels are shown in Table 4. In these analyses, a significantly lower risk for dying from severe dengue was associated with a history of previous dengue infection ($OR_{(h)}$ = 0.78), report of fever associated with 3–5 ($OR_{(h)}$ = 0.72) and 6–8 ($OR_{(h)}$ = 0.51) other early symptoms of severity, a positive tourniquet test result ($OR_{(h)}$ = 0.47) and presence of mild bleedings ($OR_{(h)}$ = 0.54). In the same analyses, a higher chance for dying was associated with delays of 5–9 days in the notification since onset of the symptoms ($OR_{(h)}$ = 1.19) and > 90 days ($OR_{(h)}$ = 2.30), and absence of fever or fever associated with one other symptom ($OR_{(h)}$ = 1.53). Patients with an unknown history of previous dengue ($OR_{(h)}$ = 2.31) and no/unknown history of tourniquet testing ($OR_{(h)}$ = 2.41) also had a higher chance of dying from severe dengue.

After we controlled for all variables in previous hierarchical levels and including those from the fourth hierarchical level, a strong positive gradient for the risk of dying from severe dengue was found with increasing number of warning signs (late signs of severity) from 2 ($OR_{(h)}$ = 2.01) to ≥ 4 signs ($OR_{(h)}$ = 11.80), among patients with high hematocrit ($OR_{(h)}$ = 2.46) and cavitary effusions ($OR_{(h)}$ = 2.15). Platelets counts between 50,001 and 100,000/mm^3 conferred protection against death from severe dengue ($OR_{(h)}$ = 0.56) compared with those with platelets counts > 100,000/mm^3 (Table 5).

Results from multivariate logistic regression analyses ignoring the hierarchy of variables were all similar to those including it.

DISCUSSION

This is the first nationwide study that investigated determinants of death from severe dengue in Brazil. Dengue is an avoidable cause of death,[18] and infection may be prevented by health promotion activities and vector control. However, once a person becomes infected, deaths may be prevented by early and appropriate diagnosis and disease management. Therefore, awareness of health care professionals is as fundamental as ready accessibility to health care services.

In our study, patients with severe dengue who were > 50 years of age had a two-fold greater chance of dying than patients < 1–14 years of age. A high dengue case-fatality rate for older adults was also found during dengue epidemics in Puerto Rico and Taiwan, and it might have been caused by co-morbidities, which are more prevalent in this age group and to a higher incidence of DSS.[19,20]

Hierarchical regression analyses showed that men had a higher chance of death from severe dengue than women. The

TABLE 4
Association between death from severe dengue and early signs of severity characteristics, Brazil, 2000–2005*

	Univariate analysis		Multivariate, Third HL			Multivariate FM		
Characteristic†	OR_C	95% CI	OR_H	95% CI	Wald test	OR_F	95% CI	Wald test
History of dengue								
No	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Yes	1.00	0.80–1.25	0.78	0.62–0.99		0.72	0.56–0.92	
Missing (15.39%)	3.04	2.64–3.51	2.31	1.91–2.79		2.31	1.92–2.78	
Fever plus symptoms‡								
Fever plus 2 symptoms	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Fever plus 3–5 symptoms	0.50	0.39–0.64	0.72	0.55–0.95		0.65	0.49–0.87	
Fever plus 6–8 symptoms	0.29	0.23–0.38	0.51	0.38–0.67		0.41	0.31–0.56	
No fever plus < 2 symptoms	1.63	1.21–2.19	1.53	1.10–2.13		1.39	0.99–1.96	
Tourniquet test result								
Negative	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Positive	0.48	0.35–0.67	0.47	0.33–0.66		0.50	0.35–0.72	
Unknown/missing (4.80%)	4.95	4.07–6.03	2.41	1.94–3.00		2.14	1.71–2.69	
Mild bleeding§								
No	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Yes	0.56	0.48–0.65	0.54	0.45–0.64		0.40	0.33–0.49	
Missing (15.16%)	1.66	1.41–1.94	0.86	0.70–1.06		0.48	0.37–0.61	
Time to notification, days								
0–4	1.00	Referent	1.00	Referent	0.02	1.00	Referent	0.004
5–9	1.16	1.01–1.34	1.19	1.02–1.40		1.31	1.11–1.55	
10–30	1.53	1.26–1.86	1.10	0.88–1.36		1.17	0.93–1.46	
31–90	2.47	1.76–3.48	1.28	0.88–1.87		1.34	0.90–2.00	
Missing (0.62%)	3.74	2.19–6.40	2.30	1.23–4.29		2.11	1.11–4.03	

*HL = hierarchical level; FM = final model ignoring the hierarchy; OR_C = crude odds ratio; CI = confidence interval; OR_H = hierarchical odds ratio; OR_F = fully adjusted odds ratio.
†Values in parenthesis are proportion of missing data in the final model (n = 12,306).
‡Headache, exanthema, retro-orbital pain, prostration, myalgia, nausea/vomiting, arthralgia, and diarrhea.
§Epistaxis, petechiae, gingival bleeding, and uterine bleeding.

TABLE 5
Association between death from severe dengue and late signs of severity variables, Brazil, 2000–2005*

Characteristic†	Univariate analysis		Multivariate, Fourth HL			Multivariate FM		
	OR_C	95% CI	OR_H	95% CI	Wald test	OR_F	95% CI	Wald test
Hematuria								
No	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Yes	1.77	1.29–2.43	1.32	0.89–1.97		1.34	0.90–1.99	
Missing (29.74%)	2.49	2.18–2.83	2.24	1.68–2.97		2.16	1.63–2.86	
Gastrointestinal bleeding								
No	1.00	Referent	–	–		–	–	
Yes	2.10	1.64–2.69	–	–		–	–	
Missing (29.93%)	2.51	2.20–2.86	–	–		–	–	
Warning signs‡								
No	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
1	1.07	0.91–1.26	1.00	0.83–1.21		1.00	0.82–1.21	
2	2.27	1.86–2.79	2.01	1.57–2.57		1.99	1.56–2.54	
3	4.15	3.11–5.53	4.86	3.36–7.02		4.82	3.34–6.96	
≥ 4	10.72	7.39–15.54	11.80	7.47–18.62		11.98	7.60–18.91	
Missing (12.61%)	1.33	1.09–1.64	0.74	0.56–0.98		0.75	0.57–0.99	
High hematocrit§								
No	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Yes	2.90	2.28–3.68	2.46	1.85–3.28		2.47	1.86–3.29	
Missing (50.30%)	2.55	2.20–2.96	1.90	1.55–2.33		1.91	1.56–2.35	
Cavitary effusions¶								
No	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
Yes	4.41	3.42–5.69	2.15	1.53–3.01		2.11	1.51–2.96	
Missing (40.23%)	1.75	1.54–2.00	1.27	0.98–1.63		1.24	0.96–1.59	
Platelets (cells/mm^3)								
> 100,000	1.00	Referent	1.00	Referent	< 0.001	1.00	Referent	< 0.001
50,001–100,000	0.75	0.51–1.12	0.56	0.36–0.87		0.56	0.36–0.86	
1,000–50,000	1.82	1.28–2.58	0.90	0.60–1.35		0.91	0.61–1.35	
Invalid data	3.27	2.43–4.41	1.69	1.18–2.42		1.69	1.18–2.41	
Missing (34.23%)	1.06	0.77–1.46	1.26	0.85–1.88		1.29	0.87–1.91	

*HL = hierarchical level; FM = final model ignoring the hierarchy; OR_C = crude odds ratio; CI = confidence interval; OR_H = hierarchical odds ratio; OR_F = fully adjusted odds ratio.
†Values in parenthesis are proportion of missing data in the final model (n = 12,306).
‡Severe abdominal pain, arterial hypotension, neurologic manifestation, painful hepatomegaly, hypovolemic shock, hepatic failure and myocarditis.
§Men (≥ 54%), women (≥ 48%), and children ≤ 14 years of age (≥ 45%), an increase > 20% between the smallest and the largest hematocrit.
¶Ascites, pleural effusion and pericardial effusion.

fact that in Brazil men seek health services less frequently and usually later than women may delay the opportunity for diagnosis and proper treatment of dengue.[21] This hypothesis is consistent with a higher overall number of deaths observed among men than women reported for Brazil, and it emphasizes not only to a biological explanation but also behavioral risk factors.[22]

Race/color classification in Brazil is based on self report.[23] Trends toward higher overall mortality rates among blacks in almost all states in Brazil have been reported.[22] It is also well known that there is a close relationship between race/color and socioeconomic status. Therefore, the association we found with deaths from severe dengue suggests more a barrier to access to quality health care rather than biological differences.[21] The significant ORs obtained for race/color in the multivariate model (first hierarchical level) (Table 2) after controlling for education, age, sex, and period of notification indicate that there must be residual effects of socioeconomic status, access to health care, and some clinical characteristic. In the final model, when all variables studied are taken into consideration, the association of outcome with race/color disappears (Table 2).

Residents of rural areas were found to have twice the risk of death from severe dengue even after controlling for all the other variables available for study (Table 3). This finding is probably caused by a higher concentration of health care services and professionals in the urban centers but could also be a reflection of socioeconomic status, or both.[21]

Higher dengue case-fatality rates were found for all regions in comparison to the West Central region, suggesting uneven regional distribution of both factors, determinants of mortality, and quality of health care. It is well known that quality of health care is influenced by the health care services management and organization, as well as level of health care professional training and coverage.[21] An unequal geographic distribution of health care resources and health care services management capability has been reported in Brazil.[22] For example, the highest median ratio of beds per 10,000 inhabitants is found in the West Central region (25.5 beds/10,000 inhabitants), followed by the Southern (23.2), Northeastern (15.0), Southeastern (12.7), and Northern (12.4) regions. These findings loosely correspond to the trend seen in risk of death from severe dengue estimated in Table 3 but would require further investigation to pinpoint all the factors actually at play. In the same way, when state of notification was different from the presumed state of infection there was a higher chance of mortality, again suggesting access barriers to health services or difficulties associated with the difference in the epidemiological context that may compromise the clinical suspicion, a fact that demands more attention in future studies.

Increased death rates from severe dengue among patients notified in non-epidemic periods and in the southern region may suggest a decrease in the clinical suspicion in places and times of lower disease incidence. This fact reinforces the need for permanent alerts in regards to dengue in all regions of country and all seasons of the year.

In this study, hospitalization was identified as a factor associated with death by severe dengue, even when controlling for

relevant variables (final model, OR = 1.59, 95% CI = 1.26–1.98). Obviously, hospitalized patients are those probably with a worse prognosis (indication bias). However, disease severity variables were controlled for in the analysis and did not completely explain away the higher mortality of these patients (residual confounding). Thus, this finding may suggest that quality of care is of complex scope encompassing more than access to health care services *per se*.

Once a diagnosis of dengue is made, a notification form is completed and sent to SINAN. The higher probability of death among patients who had their case notified after four days from onset of symptoms in comparison to those notified earlier highlights again the importance of a correct and prompt diagnosis and treatment, which is crucial in the critical stage of DHF (Table 4). The delay may be caused by lack of awareness of health care service personnel, or less than adequate care; further research may elucidate the components actually involved as well as quantify their impact.

A higher chance of death by severe dengue was observed among patients that did not have information about the history of vaccination against yellow fever, previous dengue, tourniquet tests, and laboratory dengue confirmation. This finding may suggest that lack of information may be a *proxi* for lack of access to a proper clinical history and examinations, as well as less than adequate laboratory diagnostic support.

Some early warning signs of dengue severity were identified as associated with lower chance of death, i.e., history of previous dengue, fever associated with three or more symptoms, a positive tourniquet test and the presence of mild bleeding. It is possible that these alert signs indicate an important opportunity for prompt diagnosis and adequate case management at a time early enough when treatment interventions would be most efficacious in preventing death. Rigau-Pérez[24] emphasizes that the case detection of DHF level 1 may be significantly compromised if a tourniquet test is not carried out. The results found in our study reinforce the need for implementation of standard clinical protocols for the effective diagnosis and clinical management of dengue.[25,26]

A higher chance of death among patients with high hematocrit results and presence of cavitary effusions reinforce the assumption that plasma extravasations is the main pathologic change in severe illness, and this occurrence differentiates classical dengue from DHF/DSS.[4] In addition, plasma extravasations should always alert the attending physician to the risk for DSS.[27]

In this study, persons with platelet counts of 50,000–100,000 cells/mm^3 (compared with those with higher counts) had a lower chance for dying, suggesting that this early finding may contribute to the diagnosis and should lead to prompt treatment. Early signs of severity, such as low platelet counts, may be seen as a protective factor if interpreted as an alert for health professionals, leading to prompt and adequate management of the patient. Some authors have discussed the usefulness of using a cutoff point for platelet counts of 50,000–80,000 cells/mm^3 as a criterion for hospitalization of patients with a diagnosis of dengue.[28] Our results support the contention that it would probably lead to better outcomes.

Lower education level, black/brown race/color, and rural residence are variables identified in this study as being associated with the higher chance of death by severe dengue, which could fuel the debate on the social determinants of health in Brazil. According to the National Household Sample Survey, 23% of Brazilians > 15 years of age are functionally illiterate (< 4 years of schooling); 60% of these persons are black/brown.[23] We found a higher chance of death by severe dengue in groups with social disadvantages, suggesting that differences in case-fatality rates from severe dengue go beyond biological factors and enter the realm of health iniquities, as proposed by Whitehead.[29]

Because this study was based on secondary data, some limitations must be discussed. Misclassification and missing data may not be completely ruled out. Cases were not restricted to those confirmed by laboratory tests and false-positive cases may have been included. This method decision sought to prevent selection bias from systematically excluding cases without access to laboratory diagnosis and those that occurred during the epidemic period when diagnosis is made mostly through the link between clinical presentation and the epidemiologic situation of the disease at that time.[26]

A category to allocate missing data was entered in the models when there was a relevant proportion of unknown data for a given variable. The large sample size helped to reduce random error, and use of a second logistic modeling strategy to validate the first hierarchical approach helped to improve study internal validity. Relevant factors such as chronic diseases, immunologic status, dengue virus serotype, socioeconomic level, among others, if unavailable or poorly measured, may lead to residual confounding in the study results. However, these data were not available in SINAN and we could not measure their impact. Finally, the possibility of underreporting dengue cases cannot be dismissed. However, it has been shown that underreporting of severe cases of dengue is kept to a minimum in SINAN.[30]

Because this study had excellent external validity, its results should be of great value to public health officials in identifying subgroups of severe dengue patients who are at higher risk of death and for whom close clinical follow-up should be made available. In addition, we have also uncovered important gaps in knowledge that should be addressed in future research of determinants of death from severe dengue.

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Authors' addresses: Giselle Hentzy Moraes, SHIS QI 25, Conjunto 02, Casa 09, Brasília DF, Brazil CEP 71660-220, E-mail: giselle.hm@gmail.com. Eliane de Fátima Duarte, Hospital Universitário de Brasília, CAS/DSA/DGP/UNB, SGAN 605, Av. L2 Norte, Brasilia DF-CEP 70840-901, E-mail: eliane.duarte@mcgill.ca. Elisabeth Carmen Duarte, SQSW 304, Bloco A, Apartamento 609, Setor Sudoeste Brasília DF, Brazil CEP 70673-401, E-mail: eduarte@unb.br.

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